

Breast Cancer following Breast Reduction Surgery in Sweden

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Women undergoing breast reduction surgery have been reported to be at low subsequent risk of breast cancer, especially when the surgery is performed after age 40. To evaluate the age and time-related patterns of cancer risk following surgical removal of breast tissue, we identified 31,910 women who underwent breast reduction surgery from 1965 to 1993 in Sweden using hospital discharge register data. There were 19,975 women (63 percent) under age 40 at surgery.

Linkages with Swedish registries for cancer, death, and emigration were based on unique national registration numbers assigned to each Swedish resident. Cancer incidence was contrasted with that expected in the general population based on age- and calendar year-specific data from the nationwide cancer registry.

Overall, 161 incident breast cancers were identified during 238,765 person-years of observation (mean, 7.5 years) compared with 223.9 expected (standardized incidence ratio = 0.72; 95 percent confidence interval = 0.61 to 0.84). The reduction in risk of breast cancer was most pronounced for women whose operations were performed after age 50 (SIR = 0.57) and for those followed for more than 5 years (SIR = 0.68). Among women operated on before age 40, risk was nonsignificantly elevated within the first 5 years after surgery (SIR = 1.47; 95 percent CI = 0.89 to 2.30) but tended to be reduced thereafter (SIR = 0.80; 95 percent CI = 0.55 to 1.13). The magnitude of the reduction in risk thus appears directly related to age at surgery.

Women followed for an average of 7.5 years after bilateral breast reduction surgery were at a statistically significant 28 percent decreased risk of breast cancer. The current study is thus consistent with a protective effect following partial removal of breast glandular tissue. (*Plast. Reconstr. Surg.* 106: 755, 2000.)

Recent cohort studies of women who have undergone bilateral breast reduction surgery revealed significant reductions in the subsequent risk of breast cancer, especially among

women over the age of 40 at surgery.¹⁻³ The risk of breast cancer was significantly reduced by 39 to 50 percent and was attributed to the removal of mammary glandular tissue mass. However, risk was not significantly lowered among women under the age of 40 at surgery, who comprised well over 50 percent of the women studied. Possible reasons for the absence of a protective effect among younger women included chance due to the relatively small number of incident breast cancers, the comparatively short follow-up, and different risk factors for young compared with older women who elect to have breast reduction surgery.

There has been renewed interest in offering women at high risk for breast cancer prophylactic mastectomies as an option to reduce their risk.⁴⁻⁶ Until recently, there was insufficient evidence to recommend for or against prophylactic mastectomy as a means to reduce breast cancer risk.^{7,8} One early study of 1500 women concluded that subcutaneous mastectomy was an effective means of prophylaxis, but methodologic shortcomings tempered interpretation.⁹ A recent investigation of 639 women with a family history of breast cancer, however, found a 90 percent reduction in the incidence of breast cancer following bilateral prophylactic mastectomy (median age at surgery, 42 years).¹⁰

Although women undergoing breast reduction surgery are unlikely to be strictly comparable to women undergoing prophylactic mastectomies, the possible reduction in risk

associated with partial removal of breast tissue is of biologic interest. To provide additional information on risk reduction following surgery, we assembled a nationwide cohort of more than 31,000 women in Sweden who had received breast reduction surgery from 1965 to 1993 and followed them through 1993 to determine the incidence of breast and other cancers. Our study has long follow-up, spanning 30 years, and is larger than previous investigations.

METHODS

The Swedish Inpatient Register^{11,12} was used to identify 34,476 women undergoing breast reduction surgery (procedure codes 3850–3851) between 1965 and 1993. The unique national registration number assigned to each Swedish resident permitted accurate linkage of information among various record registries. Linkage with the Swedish Register of the Total Population, the Death Register, the Swedish Cancer Register, and the Migration Register provided information on vital status, cancer incidence, and migration. These registers also allowed us to identify women with invalid national registration numbers for whom follow-up information was not available. Excluded were 715 women (2.1 percent) due to faulty entry dates in the Swedish Inpatient Register records or erroneous national registration numbers; 1 woman with surgery at 10 years of age; 1408 women with breast cancer diagnosed before entry (nearly all with reconstructive surgery); 427 women with some other form of cancer before entry; and 15 women with breast cancer diagnosed within 3 months of the procedure (i.e., during routine histopathologic examination of the resected tissue). The study cohort thus comprised 31,910 women. Because there is almost no private inpatient treatment in Sweden, hospital-provided medical services, as recorded in the Swedish Inpatient Register, are essentially population-based and referable to the county where the patient lives.

Only first cancers were evaluated among the 31,910 women who underwent breast reduction surgery, excluding cancers occurring before and within 3 months of surgery. Person-years of observation were computed beginning 3 months after the date of breast reduction surgery and ending on the date of death, the date of migration, or December 31, 1993, whichever occurred first. Expected numbers of cancers were calculated by multiplying the age

and calendar year-specific person-years of observation by the corresponding cancer incidence rates of the general Swedish population. Five-year age and calendar year categories were used throughout. Standardized incidence ratios (SIR) were computed as the ratio of observed-to-expected values and 95 percent confidence limits calculated assuming a Poisson distribution. A 95 percent confidence interval (CI) that does not contain 1.0 indicates that the standardized incidence ratio is statistically significant. No correction was made to account for multiple comparisons. A multivariate Poisson regression analysis based on the standardized incidence ratios was also conducted to evaluate the effect of age and calendar period at surgery as well as follow-up time.¹³ The model including these three variables showed only a slight overdispersion, and adjustment of the confidence limits was not considered necessary. Interactions were also tested, but none reached statistical significance.

RESULTS

The median age at breast reduction surgery was 33 years (range, 11 to 87), and the mean length of follow-up was 7.5 years (range, 0 to 30) based on 232,722 person-years of observation. Overall, 662 cancers were observed versus 729 expected (SIR = 0.91; 95 percent CI = 0.84 to 0.98) (Table I). This deficit was due primarily to a significant 28 percent reduction in breast cancer occurrence (161 observed versus 223.9 expected; SIR = 0.72; 95 percent CI = 0.61 to 0.84). Lung cancer also occurred below expectation (SIR = 0.73), as did melanoma (SIR = 0.72). Significant excesses were seen for cancers of the corpus uteri (SIR = 1.37) and tumors of endocrine organs other than the thyroid (SIR = 1.55), including parathyroid adenomas (SIR = 1.51).

Risk of subsequent breast cancer was inversely related to age at breast reduction surgery (Table II). Significantly low risks of breast cancer were most apparent among the 6639 women 50 years of age and older at surgery (SIR = 0.57; 95 percent CI = 0.4 to 0.7). Women under age 50 at surgery were also at lowered risk of breast cancer (SIR = 0.85; 95 percent CI = 0.7 to 1.0), which was accounted for by women in their 40s at the time of surgery (SIR = 0.76; 95 percent CI = 0.6 to 1.0). The inverse association of age at surgery with risk of breast cancer was also confirmed in a multivariate analysis adjusting for calendar period and

TABLE I

Standardized Incidence Ratios and 95% Confidence Intervals for Cancers Occurring among 31,910 Swedish Women Who Underwent Breast Reduction Surgery during 1965–1993

Cancer Site (ICD-7)	Observed	Expected	SIR	95% CI
All malignant neoplasms (140–209)	662	728.9	0.91	0.84–0.98
Buccal cavity and pharynx (140–148)	8	8.90	0.90	0.39–1.77
Stomach (151)	14	15.16	0.92	0.51–1.55
Colon (153)	41	42.07	0.97	0.70–1.32
Rectum (154)	16	23.54	0.68	0.39–1.10
Liver (155)	18	14.95	1.20	0.71–1.90
Lung (162)	23	31.98	0.73	0.46–1.10
Breast (170)	161	223.89	0.72	0.61–0.84
Cervix (171)	26	31.70	0.82	0.54–1.20
Corpus uteri (172)	61	44.67	1.37	1.04–1.75
Ovary (175)	40	45.34	0.88	0.63–1.20
Other and unspecified female organs (176)	6	5.00	1.21	0.44–2.63
Kidney (180)	15	16.12	0.93	0.52–1.53
Bladder (181)	16	13.21	1.21	0.69–1.97
Melanoma (190)	25	34.87	0.72	0.46–1.06
Nonmelanoma skin cancer (191)	16	11.28	1.42	0.81–2.30
Brain and nervous system (193)	28	28.96	0.97	0.64–1.40
Thyroid (194)	17	12.19	1.39	0.81–2.23
Other endocrine (195)	35	22.52	1.55	1.08–2.16
Parathyroid (195x)	25	16.52	1.51	0.98–2.23
Bone (196)	0	1.45	0.00	0.00–2.54
Connective tissue (197)	2	5.03	0.40	0.05–1.44
Lymphatic and hematopoietic (200–209)	37	41.63	0.89	0.63–1.23
Non-Hodgkin's lymphoma (200, 202)	13	18.19	0.70	0.38–1.22
Hodgkin's disease (201)	3	4.41	0.68	0.14–1.99
Multiple myeloma (203)	7	6.76	1.04	0.42–2.13
All leukemia (204)	14	12.10	1.16	0.63–1.94

follow-up time. Among the 19,975 women under age 40 at resection, there was no overall difference in observed versus expected breast cancers (52 compared with 52.5), although risks varied over time since surgery among these young women. In this group, a nonsignificantly elevated risk within 5 years of surgery ($SIR = 1.47$; 95 percent $CI = 0.89$ to 2.30) was balanced by a tendency toward a reduced risk more than 5 years after surgery ($SIR = 0.80$; 95 percent $CI = 0.55$ to 1.13), suggesting a lowering of risk among young women in the long but not the short term, although the reduction after 10 years was slight.

The risk of breast cancer was further evaluated by ages at follow-up after the surgical procedure (Table III). A significant lowering of risk occurred in later life, notably among the women observed after age 50 (91 compared with 150.2). Among women observed under age 40 at follow-up, there were 16 breast cancers compared with 18.0 expected.

DISCUSSION

Our nationwide study of more than 31,000 women who received breast reduction surgery for functional and/or cosmetic reasons provides further evidence that removal of glandu-

lar and surrounding tissue may lower the subsequent risk of breast cancer. Age at operation was the primary determinant of subsequent breast cancer risk, with the overall reduction seen predominantly in women who were 40 years of age or older. The reduction in risk was 24 percent and 43 percent for women between 40 and 49 and over age 50 at surgery, respectively. An inverse association between age at surgery and breast cancer risk, independent of calendar period and follow-up time, was verified in an internal multivariate analysis. No overall lowering of breast cancer risk relative to the general population was apparent for women under the age of 40 years when treated, although they did show a 20 percent reduction in risk in the long term (more than 5 years since surgery). That breast cancer risk was reduced within the first 5 years after surgery for women over age 40, and after 5 years for younger women, suggests that extended follow-up might be required to detect a protective effect among the young (i.e., they must live to the ages later in life when breast cancer rates are elevated). This possibility was consistent with a multivariate analysis showing a tendency, albeit nonsignificant, toward falling rel-

TABLE II

Standardized Incidence Ratios and 95% Confidence Intervals for Breast Cancer among 31,910 Swedish Women Who Underwent Breast Reduction Surgery during 1965–1993 by Age at Surgery and Time after Surgery

Age at Surgery, Years (<i>n</i> = number of women)	Time after Surgery (years)	Breast Cancer		SIR	95% CI
		Observed	Expected		
20–29 (<i>n</i> = 13,769)	<1	0	0.21	0.00	0.00–17.6
	1–4	5	1.80	2.89	0.94–6.73
	5–9	1	3.79	0.29	0.01–1.61
	≥10	8	9.94	0.80	0.34–1.59
	TOTAL	14	14.17	0.99	0.54–1.66
30–39 (<i>n</i> = 5825)	<1	0	1.51	0.00	0.00–2.44
	1–4	14	9.40	1.50	0.81–2.50
	5–9	8	12.75	0.63	0.27–1.24
	≥10	16	14.67	1.09	0.62–1.77
	TOTAL	38	38.33	0.99	0.70–1.36
40–49 (<i>n</i> = 5296)	<1	4	4.88	0.82	0.22–2.10
	1–4	22	23.20	0.95	0.59–1.44
	5–9	11	19.93	0.55	0.28–0.99
	≥10	13	18.10	0.72	0.38–1.23
	TOTAL	50	66.11	0.76	0.56–1.00
≥50 (<i>n</i> = 6639)	<1	3	9.39	0.32	0.07–0.94
	1–4	23	40.93	0.56	0.36–0.84
	5–9	22	31.92	0.69	0.43–1.04
	≥10	11	21.50	0.51	0.26–0.92
	TOTAL	59	103.68	0.57	0.43–0.73
All (<i>n</i> = 31,910)	<1	7	15.94	0.44	0.18–0.90
	1–4	64	75.33	0.85	0.65–1.08
	5–9	42	68.41	0.62	0.44–0.83
	≥10	48	64.21	0.75	0.55–0.99
	TOTAL	161	223.9	0.72	0.61–0.84

ative risks with time after breast reduction surgery, regardless of age at surgery.

Our findings are consistent with previous studies indicating that surgery to reduce breast size is associated with a lower breast cancer risk later in life.^{1–3,14} A nationwide study of 7720 women in Denmark whose breasts were surgically reduced from 1977 to 1992 revealed a 50 percent overall lowering of breast cancer risk.² A reduction in risk, however, was not detected among women under age 40 at surgery. Another nonoverlapping study in Denmark with

much longer follow-up reported a lowered risk (RR = 0.6) among 1240 women surgically treated for breast hypertrophy between 1943 and 1971.¹ Risk was reduced by about 30 percent among women under age 40 at surgery, but not significantly (24 compared with 30.4). A relationship between the amount of tissue removed and subsequent decreases in breast cancer risk was also reported.¹

A recent study of 26,567 women in Ontario, Canada who underwent bilateral breast reduction surgery between 1979 and 1992 also found

TABLE III

Standardized Incidence Ratios and 95% Confidence Intervals for Breast Cancer among 31,910 Swedish Women Who Underwent Breast Reduction Surgery during 1965–1993 by Age Attained at Follow-Up

Age at Follow-Up (years)	Breast Cancer		SIR	95% CI
	Observed	Expected		
<30	3	1.79	1.68	0.35–4.90
30–	13	16.16	0.80	0.43–1.38
40–	54	55.73	0.97	0.73–1.26
50–	39	67.14	0.58	0.41–0.79
60–	38	63.83	0.59	0.42–0.82
≥70	14	19.24	0.72	0.40–1.22
Total	161	223.89	0.72	0.61–0.84

a 39 percent lowering of breast cancer risk (101 compared with 165.8) but no evidence for an effect of age at surgery.³ However, among the 12,000 Canadian women who were under age 40 at the time of surgery, only eight breast cancers were reported, and the follow-up (6.5 years on average) may have been too short to demonstrate a significant reduction in risk in this group. The authors also mentioned the possibility that out migration from the reporting areas in Ontario to other parts of Canada might have resulted in an under-ascertainment of cases.

The three cohorts of women undergoing breast reduction surgery in Denmark and Sweden are compared and combined in Table IV. The Canadian publication did not provide a detailed distribution of breast cancer risk by age at surgery so could not be included. Age at surgery is seen to be related to a reduced risk of subsequent breast cancer, reaching 50 percent for women over age 50 at surgery. There was little overall variation in the apparent protective effect of breast reduction by time after surgery except among young women. In both Denmark and Sweden, breast cancer risk was elevated within 5 years of surgery (SIR = 1.44) among women treated under age 40, but longer follow-up revealed a reduction in risk (SIR = 0.79) (Table V).

The age differences we observed in risk reduction may relate in part to issues of follow-up or to variations in the characteristics of women who elect to have reduction surgery. Because the rates of breast cancer remain low until the later years of life, a protective effect of breast tissue removal may take longer to become evident in younger women, underscoring the

need for long-term follow-up. Alternatively, women who had breast reduction surgery after age 50 are somewhat less apt to have a familial or genetic disposition to getting breast cancer than younger women, and accordingly the surgical procedure may be more effective.

Constitutionally, very young women undergoing this procedure have been reported to be slim with large breasts, while older women tend to be obese.¹ There is some evidence that breast size is correlated with the risk of postmenopausal breast cancer but primarily among those who were thin as young women.¹⁵ Obesity is associated with a lowered risk of breast cancer in premenopausal women¹⁶ but an elevated breast cancer risk in postmenopausal women.¹⁷ Thus, younger women who are slim and older women who are obese may both be at higher underlying risk of breast cancer than the general population. If true, then the apparent reduction in risk seen after surgical removal of breast tissue might be greater than indicated by comparisons with the general population.

Clinical series have reported the detection of occult breast cancers in 0.16 to 0.38 percent of pathology specimens examined after reduction surgery.¹⁸ The recent Canadian breast reduction study diagnosed breast cancer in 0.06 percent of the pathologic specimens examined.¹⁹ In Sweden, all surgical departments submit resected tissues for histopathologic review, and a similar prevalence of detected breast cancer (0.05 percent) was found. Among the 31,910 surgeries, 15 were found to have breast cancer based upon this evaluation, of which none was carcinoma in situ, and these women were excluded from follow-up. While reducing tissue mass may thus lower breast cancer risk by elim-

TABLE IV
Incidence of Breast Cancer versus Incidence Expected following Breast Reduction Surgery in Three Cohort Studies from Denmark (Baasch 1996; Boice 1997) and Sweden (Current Study)

	Denmark (Baasch 1996) (<i>n</i> = 1240) 1943–1971		Denmark (Boice 1997) (<i>n</i> = 7720) 1977–1992		Sweden (Current Study) (<i>n</i> = 31,910) 1965–1993		Combined Studies (<i>n</i> = 40,870)			
	Obs	Exp	Obs	Exp	Obs	Exp	Obs	Exp	SIR	95% CI
Age at surgery (years)										
<30	13	15.38	4	3.1	14	14.17	31	32.65	0.95	0.65–1.35
30–39	11	15.00	9	10.5	38	38.33	58	63.83	0.91	0.69–1.17
40–49	5	14.86	9	16.7	50	66.11	64	97.67	0.66	0.50–0.84
≥50	3	7.28	7	23.7	59	103.68	69	134.66	0.51	0.40–0.65
All	32	52.55	29	53.9	161	223.9	222	330.35	0.67	0.59–0.77
Time after surgery (years)										
<10	5	7.16	21	44.0	113	159.7	139	210.86	0.66	0.55–0.78
≥10	27	45.39	8	9.9	48	64.21	83	119.50	0.70	0.55–0.86

TABLE V

Incidence of Breast Cancer versus Incidence Expected following Breast Reduction Surgery in Two Cohort Studies from Denmark (Boice 1997) and Sweden (Current Study) among Women under Age 40 at Surgery

Age at Surgery (years)	Time after Surgery (years)	Denmark (Boice 1997)		Sweden (Current Study)		Combined			
		Obs	Exp	Obs	Exp	Obs	Exp	SIR	95% CI
10-29	<5	1	0.6	5	2.01	6	2.61	2.30	0.84-5.00
	≥5	3	2.5	9	13.73	12	16.23	0.74	0.38-1.29
30-39	<5	5	3.3	14	10.91	19	14.21	1.34	0.80-2.09
	≥5	4	7.1	24	27.42	28	34.52	0.81	0.54-1.17
All	<5	6	3.9	19	12.92	25	16.82	1.49	0.96-2.19
	≥5	7	9.6	33	41.15	40	50.75	0.79	0.56-1.07

inating cells destined to develop into cancer,²⁰⁻²² it is also possible that removal of adipose and periductal stromal tissue contributes to the lowered risk through changes in the microenvironment of terminal duct-lobular units. Human mammary lipid samples obtained from women undergoing elective reduction mammoplasty, for example, have been found to possess genotoxic activity that might bear on the etiology of breast cancer.²³

Among the 1408 women excluded from the cohort because of a prior history of breast cancer, 41 subsequently developed contralateral breast cancer as compared with 17.3 expected, consistent with the high risk of second primary cancers seen in population studies of women with breast cancer.²⁴

Strengths of our study include the very large numbers, the nearly complete inclusion of all women who underwent breast reduction surgery in Sweden, and the nearly complete follow-up for breast cancer incidence. Further, no remarkable differences were seen in the risks for other forms of cancer after breast reduction surgery, although the slight increase in cancer of the corpus uteri is consistent with an effect of obesity,²⁵ while the nonsignificant decrease in cancer of the lung suggests a lower frequency of smoking. The reduced risk seen for melanoma also suggests that these women might be more health conscious or less likely to sunbathe than women in the general population.

Weaknesses of our study include the absence of information on possible confounding factors such as reproductive history, menarche, and family history. It is possible that women electing breast reduction surgery may deviate from the general population used for comparison in terms of parity, age at first pregnancy, body fat patterns, socioeconomic level, lifestyle characteristics, or medical conditions prompt-

ing surgery, such as cosmetic problems, back pain, and breast hypertrophy. In addition, the follow-up (7.5 years on average) may not have been sufficient to demonstrate convincingly a temporal gradient in the reduction in risk among young women who underwent breast reduction surgery and who have not yet reached the ages later in life when breast cancer becomes more common. Another shortcoming is that we do not know how much tissue was removed, but this information will be obtained in an ongoing nested case-control study within this cohort. Preliminary analysis, however, indicates that the reduction in breast cancer risk was directly related to the amount of breast tissue removed as previously reported.¹

Women undergoing reduction mammoplasty in Sweden did not routinely receive mammograms before surgery, thus minimizing the likelihood that preoperative procedures removed women with breast cancer from the cohort. A recent survey of all seven departments of plastic surgery, which performed about one-half of all reduction mammoplasties from the 1960s through the 1980s, revealed that five departments never conducted preoperative mammography, whereas two did if the patient was 30 years of age or older. Nonetheless, the greater risk of breast cancer in older women might have resulted in more thorough prescreening procedures such as palpation than in young women. On the other hand, preoperative evaluation, including self-breast examination, physician examination, and x-ray mammography, did not detect any breast cancers in a recent series of 2576 breast reduction patients, in contrast to four breast cancers (0.16 percent) detected in the surgical specimens.¹⁸ Increased access to mammography screening was suggested as one possible reason

for the low preoperative detection of breast cancers in recent times.

Although few clinical investigations have convincingly evaluated the efficacy of prophylactic mastectomy,⁷ a recent cohort study from the Mayo Clinic revealed a 90 percent reduction in the subsequent risk of breast cancer among 639 women at high risk of breast cancer on the basis of family history.¹⁰ A substantial reduction in risk among women under the age of 40, nearly half the cohort, was apparent in that no breast cancers was observed in this group after 14 years of follow-up on average.²⁶ However, neither subcutaneous nor simple mastectomy has been shown to provide complete protection against breast cancer development, since it is not possible to remove 100 percent of breast tissue by mastectomy. Further, the overall benefit of prophylactic mastectomy in reducing mortality associated with breast cancer may be small when viewed in absolute terms (e.g., only 1 in 25 women benefited from the surgical removal of both breasts).²⁷ Although not directly comparable, nonetheless, our series might provide additional reassurance to women without breast cancer who, because of a familial or genetic predisposition, elect to have prophylactic mastectomy to reduce risk. The fact that significant reductions in risk were seen when relatively small amounts of breast parenchyma are removed suggests that removing larger amounts will be even more beneficial. Further work is needed, however, to evaluate the benefits of surgical procedures among the very young and quantify the reduction in risk in terms of amount of tissue removed.

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